



Atlantic Provinces Pediatric Hematology Oncology Network
Réseau d'Oncologie et Hématologie Pédiatrique des Provinces Atlantiques

*Reviewed and approved by specialists at the IWK Health Centre, NS, and the
Janeway Children's Health and Rehabilitation Centre, NL*

Guidelines for Asparaginase Administration

Asparaginase is an antineoplastic agent used most effectively and commonly in pediatrics in the treatment of acute lymphocytic leukemia (ALL), lymphoblastic lymphoma, and acute myeloid leukemia (AML).

Types of Asparaginase:

- 1) asparaginase: a) *Escherichia coli* (E. coli) b) *Erwinia chrysanthemi* (or caratovora)
- used only if a hypersensitivity reaction to E.coli asparaginase occurs
Synonyms/Trade names: L-asparaginase, L-ASP, LASP, A-ase, ASN-ase, Elspar®, Kidrolase®
- 2) polyethylene glycol (PEG) asparaginase - a pegylated E. coli where strands of polyethylene glycol are attached to E. coli to prevent recognition by the immune system and thus delay clearance
Synonyms/Trade names: pegaspargase, PEG-asparaginase, PEG L-asparaginase, Oncaspar®

The initial type of asparaginase used is dependent on the protocol or treatment plan. Changes may be necessary because of hypersensitivity reactions or availability. Changes will be determined by a pediatric hematologist/oncologist.

Toxicities/Side Effects: The risk of toxicities/side effects necessitate careful monitoring when using asparaginase.

- ***Allergic/hypersensitivity reactions (HSRs):*** Reactions can range from local reactions (more common) to anaphylactic reactions, including skin rash, erythema, swelling, urticaria, pruritus, arthralgia, bronchospasm, wheezing, laryngeal edema, hypotension, respiratory and/or cardiovascular collapse and death. The mechanism of HSRs to asparaginase is thought to be related to the production of IgE or other antibodies by the polypeptide component of asparaginase which is of bacterial origin. Reactions are usually immediate, occurring 30-60 minutes after intramuscular (IM) administration, but can be delayed. Milder degrees of type I reactions can still occur up to several hours to days after treatment.

Toxicities/Side Effects (continued):

- Asparaginase HSRs are more common in adults than children. Intramuscular (IM) administration decreases the risk of anaphylaxis compared to intravenous (IV) administration. The BC Cancer Agency Cancer Drug Manual (2001) reports asparaginase produces HSRs in 6- 43% of all patients with a reduction to 6-18% in children with IM injection. The mortality rate from anaphylaxis is 1%.
 - HSRs are directly related to the number of previous asparaginase doses administered and any previous reactions to asparaginase products. Note that anaphylaxis may occur with the first exposure but is more common after successive doses. Therefore, careful monitoring must continue with each successive dose. The risk of reactions is also greater when the patient is not receiving concomitant steroids, a one month or greater period of time has elapsed since the last dose was given, the patient has a history of an allergy, and/or with higher doses.
 - Hypersensitivity reactions may necessitate the discontinuation of E. Coli asparaginase and substitution with Erwinia asparaginase. Those who react to Erwinia asparaginase may switch to PEG-asparaginase and usually tolerate it well. PEG-asparaginase may decrease, although not eliminate the risk for an HSR and reactions are often milder. Depending upon the history and severity, reactions to PEG-asparaginase may be managed by subsequently omitting PEG-asparaginase, switching to Erwinia or premedicating.
- **Coagulation abnormalities:** Asparaginase decreases fibrinogen and other clotting factors - antithrombin III (ATIII), protein C, protein S, factors II, V, VII, VIII, and VWF multimers, and can prolong prothrombin (PT) and partial prothrombin (PTT). Hemorrhagic and thrombotic events most commonly affect the CNS. Symptoms may include headache, alterations in mental status, hemiparesis, and seizures. Deep vein thrombosis affecting extremities can cause local pain, swelling or discolouration.
- **Pancreatitis** may present as abdominal tenderness or mid-epigastric pain with posterior radiation with vomiting. Severe pancreatitis may be associated with electrolyte disturbance, hypotension and a sepsis like picture. Any episode of asparaginase associated pancreatitis necessitates permanent cessation of asparaginase usage.
- **Hyperglycemia** is usually a transient side effect that occurs in about 10% of leukemic children treated with asparaginase and prednisone. Risk is higher if > 10 years old, obese, family history of diabetes mellitus, or Down Syndrome. Insulin may be required to control hyperglycemia.
- **Cerebral dysfunction** is reported in literature as common, but in children is rarely seen. Signs and symptoms can include drowsiness, lethargy, confusion, depression, hallucinations, EEG changes or seizures. Significant dysfunction in children mandates ruling out of intracranial hemorrhage or thrombosis.
- **Hepatotoxicity:** Liver enzyme abnormalities are seen occasionally, but are transient. Severe hepatotoxicity is rare.
- **Nausea and vomiting** are reported as occasional in adults but are rare in children.
- **Hyperuricemia:** Tumour lysis is seen in the rapid breakdown of large tumours sensitive to chemotherapy. Hyperuricemia may occur during initial treatment with chemotherapy and may be minimized with prophylactic use of allopurinol, hydration and sodium bicarbonate.

- **Asparaginase** is not cytotoxic to bone marrow stem cells, oral and G.I. tract mucosa, or hair follicles. Renal toxicity is very rare.

Intervention Guidelines for Hypersensitivity Reactions [as adapted from Fisher, Knobf, Durivage and Beaulieu (2003)]:

- Carefully assess patients for clinical signs and symptoms.
- Have emergency drugs available and accessible (as detailed below).
- Stop administration (if applicable). Notify the physician.
- Assess airway, breathing, circulation. Monitor vital signs.
- Maintain (or initiate) intravenous (IV) access. Administer emergency drugs as per standing or physician order. Have quick access to resuscitation equipment.
- Administer O₂ as needed and IV fluids as ordered (for hypotension).
- If wheezing or respiratory distress persists, consider nebulized salbutamol (Ventolin®).
- Based on the severity of the reaction, continue to monitor for a prolonged or biphasic anaphylactic reaction. Consider overnight monitoring for all moderate to severe PEG-asparaginase reactions.
- Document reaction, treatment and response. Report to the subspecialty complexity/tertiary care centre.

Before Administering Asparaginase:

- **Baseline lab monitoring to include:**
 - CBC - Platelets must be > 20,000/μL before administration of an IM injection.
 - urine glucose to assess hyperglycemia - if positive, do a serum glucose
 - liver function tests at beginning of each phase of treatment and at indicated times as per roadmap/protocol
 - kidney function tests at beginning of each phase of treatment and at indicated times as per roadmap/protocol
 - uric acid, electrolytes, calcium, phosphorus, albumin, amylase at diagnosis and as required
 - other lab tests as may be specified by protocol
 - no routine monitoring of coagulation parameters unless patient is symptomatic
- **Emergency equipment and drugs on hand:**
 - age/size appropriate resuscitation equipment
 - oxygen and suction
 - IV access and 0.9% NaCl
 - epinephrine 1:1,000 solution
 - diphenhydramine (Benadryl®)
 - injectable corticosteroids - hydrocortisone sodium succinate or methylprednisolone
 - patient specific orders - see IWK Health Centre preprinted physician's order, Pediatric Hematology/Oncology Protocol for Hypersensitivity Reactions
- **Assess need for prophylactic drugs:**
 - Determine need for diphenhydramine or acetaminophen pre administration. If a mild local reaction has previously occurred, an antihistamine (e.g., diphenhydramine, Benadryl®) and possibly acetaminophen may have been ordered pre further administrations. This decision should be made only in consultation with a pediatric hematologist/oncologist.

- The need for prophylactic use of allopurinol, hydration and sodium bicarbonate to prevent hyperuricemia from possible tumour lysis at initial administration will be determined at the tertiary care centre by a pediatric hematologist/oncologist.

Administration:

- IV or IM injection - IV administration is the recommended route of administration for PEG asparaginase for the Atlantic Provinces pediatric populations unless otherwise specified by the treatment protocol being followed for each patient.
- Patients who have a hypersensitivity reaction to PEG asparaginase will then be treated with IM Erwinia.
- The initial type, dose, and dosing interval of asparaginase are dependent on the protocol or treatment plan. Changes may be necessary because of hypersensitivity reactions or availability. Changes will be determined by a pediatric hematologist/oncologist.
- Asparaginase must be given in at least an intermediate complexity level of care facility and a physician must be readily available.
- Do not use a filter during IV or IM administration. Use of a 0.2 micron filter results in loss of potency.
- Reconstitute asparaginase powder in normal saline to reduce the amount of pain on injection.
- Asparaginase must be administered by a qualified health professional using established policies for safe handling of cytotoxic drugs.
- Administer using established policies for IM injections for a child, with attention to appropriate sites and maximum volumes.
- Administer IV PEG asparaginase over 1 to 2 hours. Administer through the tubing of a freely infusing solution of D5W or 0.9% NaCl or add to a 100 mL bag of 0.9% NaCl.

Monitoring Post Injection:

- The patient should be kept on the nursing unit and monitored for adverse reactions for one (1) hour post E. coli and Erwinia asparaginase injections, and two (2) hours post PEG asparaginase injections.
- Laboratory monitoring:
 - twice weekly CBC - Assess need for platelet transfusion before administration.
 - twice weekly urine for glucose - If positive for glucose, check serum glucose. If serum glucose increased, contact the pediatric hematologist/oncologist at the subspecialty complexity/tertiary care facility to discuss possible interventions (monitoring, dietician referral, endocrinologist referral, insulin). Administration of asparaginase need not be held but treatment instituted as soon as appropriate.
 - serum amylase if symptomatic of pancreatitis - Consult the pediatric hematologist/oncologist if symptomatic and/or level elevated.
 - liver function tests at indicated times as per roadmap/protocol or physician determination
 - other lab tests as may be specified by protocol
 - no routine monitoring of coagulation parameters unless patient is symptomatic

Included:

- IWK Health Centre Pediatric Hematology/Oncology Protocol for Hypersensitivity Reactions Pre-printed Physician's Order
- IWK Health Centre Pediatric Hematology/Oncology Protocol for Routine Transfusion Pre-printed Physician's Order
- IWK Pharmacy Department Asparaginase Chemotherapy Information sheet (patient/family teaching handout)

References:

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